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ORIGINAL ARTICLE

Potent Anticoagulants are Associated with a Higher All-Cause Mortality Rate After Hip and Knee Arthroplasty

Nigel E. Sharrock BMedSci, MB, ChB, Alejandro Gonzalez Della Valle MD, George Go BS, Stephen Lyman PhD, Eduardo A. Salvati MD

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Abstract Anticoagulation for thromboprophylaxis after THA and TKA has not been confirmed to diminish all-cause mortality. We determined whether the incidence of all-cause mortality and pulmonary embolism in patients undergoing total joint arthroplasty differs with currently used thromboprophylaxis protocols. We reviewed articles published from 1998 to 2007 that included 6-week or 3-month incidence of all-cause mortality and symptomatic, nonfatal pulmonary embolism. Twenty studies included reported 15,839 patients receiving low-molecular-weight heparin, ximelagatran, fondaparinux, or rivaroxaban (Group A); 7193 receiving regional anesthesia, pneumatic compression, and aspirin (Group B); and 5006 receiving warfarin (Group C). All-cause mortality was higher in Group A than in Group B (0.41% versus 0.19%) and the incidence of clinical nonfatal pulmonary embolus was higher in Group A than in Group B (0.60% versus 0.35%). The incidences of all-cause mortality and nonfatal pulmonary embolism in Group C were similar to those in Group A (0.4 and 0.52, respectively). Clinical pulmonary embolus occurs despite the use of anticoagulants. Group A anticoagulants were associated with the highest all-cause mortality of the three modalities studied.

Level of Evidence: Level III, therapeutic study. See the Guidelines for Authors for a complete description of levels of evidence.

Each author certifies that he or she has no commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.

N. E. Sharrock (✉), G. Go
Department of Anesthesiology, Hospital for Special Surgery, 535 East 70th Street, New York, NY 10021, USA
e-mail: sharrockn@hss.edu

A. Gonzalez Della Valle, E. A. Salvati
Department of Orthopaedic Surgery, Hospital for Special Surgery, New York, NY, USA

S. Lyman
Foster Center for Clinical Outcome Research, Hospital for Special Surgery, New York, NY, USA

Introduction

Perioperative anticoagulation is prescribed after THA and TKA to reduce the risk of thromboembolic disease, more specifically the risk of dying from pulmonary embolism (PE) [2, 20, 43, 50, 51, 58]. The incidence of fatal PE was as high as 2.2% (26 of 1174) in the 1960s [27]. The use of anticoagulation is believed to have reduced the incidence of symptomatic and fatal PE in the early era of total joint arthroplasty [10, 27].

During the last decade, in patient populations ranging from 1947 to 130,000, the reported incidence of fatal PE has decreased substantially to a rate of 0% to 0.2% [16, 21, 39]. This is a result of advancements in anesthesia, surgical technique, perioperative care and our better understanding of the pathogenesis of thromboembolic disease during and after surgery [11, 24, 25, 56]. The current low incidence of symptomatic and fatal PE raises the question of whether potent anticoagulation is warranted because these agents have potential side effects from bleeding [2, 7, 20, 42, 49, 58].

The numerous current thromboprophylaxis protocols in use can be classified into three groups: (1) those that rely on the use of potent anticoagulants (low-molecular-weight heparin, ximelagatran, fondaparinux, or rivaroxaban); (2) those that target venous stasis, endothelial damage, and hypercoagulability (Virchow's triad) during the period at risk for thromboembolism and rely on the use of epidural anesthesia, pneumatic compression devices, and aspirin in the majority of patients without predisposing factors for PE, the so-called multimodal prophylaxis [53]; and (3) those that rely on slow-acting oral anticoagulants (warfarin).

Because of the low incidence of fatal PE and the availability of multiple prophylaxis regimens, a prospective uni- or multicenter study evaluating the rate of fatal PE with different forms of prophylaxis may not be feasible. Moreover, because anticoagulation carries a risk of fatal bleeding complications [13, 22], all-cause mortality appears a more appropriate marker for comparison because mortality incorporates all cost-benefit effects of prophylaxis.

To overcome these limitations, we conducted a systematic review of all peer-reviewed publications in the English language during the last 9 years to represent current surgical, anesthetic, and perioperative care. We asked the following question: Do the rates of all-cause mortality and symptomatic PE differ among the three previously described thromboprophylaxis regimens?

Materials and Methods

We conducted a review of all articles published in English from 1998 to 2007. The articles were obtained using a Medline Ovid search with the following strategy. First, a search was done based on the following criteria: "thromboembolism/pc or venous thrombosis/pc or thromboprophy laxis.mp.," which yielded 7448 results. A second search was done with the following criteria: "(hip or knee).mp. [mp=title, original title, abstract, name of substance word, subject heading word]," which yielded 127,744 results. Third, the first and second searches were combined resulting in 986 studies. Finally, these studies were filtered to limit the search to publications between 1998 and 2007, resulting in 618 publications. Blinded abstracts of all 618 articles were reviewed by the senior author (NES) to determine whether 6-week or 3-month mortality and the form of thromboprophylaxis were reported. We included series with elective unilateral or bilateral THA and TKA, as well as revision arthroplasty. Series that studied specific cohorts, such as patients with cirrhosis, renal failure, obesity, or exclusively bilateral joint arthroplasty, were excluded. To capture scientifically rigorous data with a high level of evidence, and relevant to the end points of our study, we excluded personal communications, expert opinions, and studies focusing only on deep venous thrombosis as the end point. Patients had to have been operated on during the last 15 years (1991 onward) because we believe this represented current practice (including modern anesthesia, surgical and rehabilitation techniques) and coincides with the introduction of low-molecular-weight heparins to clinical practice. Only consecutive case series with documented patient followup and randomized trials were included. We excluded series in which 6-week or 3-month all-cause mortality was not available. When 3-month mortality was not reported but appeared likely to have been collected, the authors were contacted to provide the information. The authors of four publications responded with the necessary information [31, 33, 45, 57], and the remaining three studies [1, 4, 9] were excluded from the analysis.

Using these inclusion and exclusion criteria, we identified 20 publications (Table 1) [3, 6–8, 12, 14, 15, 21, 22, 31–34, 37, 38, 45, 49, 54, 59, 60] and divided them into three categories according to the antithromboembolic prophylaxis regimen given: (1) low-molecular-weight heparin, ximelagatran, fondaparinux, or rivaroxaban (Group A); (2) a multimodal prophylaxis (Group B); or (3) warfarin (Group C). All studies belonging to the three categories were further divided into 6-week and 3-month followups. Multimodal prophylaxis (Group B) was defined as a protocol consisting of intention to use regional anesthesia (epidural or spinal) with or without intraoperative heparin during surgery or pneumatic compression and aspirin after surgery. These cohort studies also included use of warfarin in 8% of the patients (570 of 7193) (those with a high risk of thromboembolism or those who received anticoagulants for medical reasons before surgery) and inevitably regional anesthesia was not feasible in all cases, so general anesthesia was used in 6% of the patients (438 of 7193). Pneumatic compression devices were used in all cases and intraoperative heparin in one study for THA [21]. Patients in Groups A (potent anticoagulants) and C (warfarin) did not receive pneumatic compression or aspirin after surgery. In five of the publications [8, 14, 34, 37, 49], the type of anesthetic was not specified for Group A (potent anticoagulants) or C (warfarin). In publications in which anesthesia was identified, 36% (3785 of 10,437) of patients in Group A (potent anticoagulants) and 29% (397 of 1342) of patients in Group C (warfarin) received spinal or epidural anesthesia.

Statistical analysis focused on the pooling of results from the included studies (Table 1). Fixed and random effects are modeling techniques used in meta-analyses and are estimates based on the assumption that (1) all possible studies are included in this analysis (fixed effects) and (2) the studies in this analysis represent a subset of a larger pool of studies (random effects). Results from both are presented to give a range of possible outcomes. The models in this case were used to calculate estimated mortality and PE rates, as well as relative risk estimates for these rates. Relative risks of these effects were calculated along with 95% confidence intervals and p values. All analyses were conducted using the SAS 9.0 for Windows (Cary, NC) and

Table 1. Summary of the studies included in the analysis

Study	Year	Modality	Hip or knee	Number of patients	Number of deaths	Death rate (%)	Number of PEs	PE rate (%)	Followup	Mean age (years)	Dates of enrollment	Study type	Consecutive versus selected
Leclerc et al. [34]	1998	A	Hip, knee	1984	12	0.60	24	1.21	3 months	67	9/1993 to 12/1994	P, non-R	S
Colwell et al. [8]	1999	A	Hip	1516	9	0.59	15	0.99	3 months	64	10/1993 to 4/1996	P, R	C
Lindahl et al. [37]	1999	A	Hip, knee	645	4	0.62	2	0.31	3 months	70	9/1994 to 5/1996	P, non-R	C
Heit et al. [22]	2000	A	Hip, knee	1195	6	0.50	9	0.75	3 months	65	11/1994 to 11/1997	P, R	S
Bauer et al. [3]	2001	A	Knee	1034	5	0.48	6	0.58	6 weeks	67	12/1998 to 1/2001	P, R	S
Samama et al. [54]	2002	A	Hip	643	0	0.00	0	0.00	6 weeks	66	9/1997 to 10/1999	P, R	S
Lassen et al. [32]	2002	A	Hip	2273	6	0.26	6	0.26	6 weeks	66	12/1998 to 1/2001	P, R	C
Turpie et al. [59]	2002	A	Hip	2257	9	0.40	13	0.58	6 weeks	67	12/1998 to 1/2001	P, R	S
Colwell et al. [6]	2003	A	Hip	1816	2	0.11	9	0.50	6 weeks	64	3/2000 to 4/2001	P, R	S
Colwell et al. [7]	2005	A	Knee	1151	7	0.61	3	0.26	6 weeks	67	6/2002 to 4/2003	P, R	S
Turpie et al. [60]	2005	A	Knee	104	0	0.00	0	0.00	6 weeks	66	2/2004 to 11/2004	P, R	S
Eriksson et al. [15]	2006	A	Hip	132	0	0.00	NR	—	6 weeks	65	1/2004 to 8/2004	P, R	S
Leali et al. [33]	2002	B	Hip	200	0	0.00	0	0.00	3 months	59	1/1997 to 10/2000	P, non-R	C
Ragucci et al. [45]	2003	B	Knee	100	0	0.00	0	0.00	3 months	66	1/1997 to 3/2001	P, non-R	C
Lachiewicz et al. [31]	2004	B	Knee	423	1	0.24	1	0.24	3 months	67	4/1999 to 3/2003	P, non-R	C
Gonzalez Della Valle et al. [21]	2006	B	Hip	1947	1	0.05	12	0.62	3 months	65	8/1994 to 7/2003	P, non-R	C
Dorr et al. [12]	2007	B	Hip, knee	1050	3	0.29	3	0.29	3 months	65	1/2002 to 7/2003	P, non-R	C
Lotke and Lonner [38]	2006	B	Knee	3473	9	0.26	9	0.26	6 weeks	NR	6/1995 to 6/2005	P, non-R	C
Colwell et al. [8]	1999	C	Hip	1495	10	0.67	12	0.80	3 months	64	10/1993 to 4/1996	P, R	C
Samama et al. [54]	2002	C	Hip, knee	636	2	0.31	4	0.63	6 weeks	66	9/1997 to 10/1999	P, R	S
Sachs et al. [49]	2003	C	Knee	957	1	0.10	1	0.10	3 months	NA	1995 to 2000	Re, non-R	C
Colwell et al. [7]	2005	C	Knee	1148	3	0.26	5	0.44	3 months	67	6/2002 to 4/2003	P, R	S
Enyart and Jones [14]	2005	C	Hip, knee	770	4	0.52	4	0.52	3 months	NA	5/2001 to 9/2002	P, non-R	S

PE = pulmonary embolism; NR = not reported; NA = Not available; P = prospective; Re = Retrospective; R = randomized; S = selected; C = consecutive.

Comprehensive Meta-Analysis (Englewood, NJ). A p value of < 0.05 was considered significant.

Results

All-cause mortality was lower in patients receiving Group B thromboprophylaxis (multimodal; 14 of 7193 [0.19%]) than Group A (potent anticoagulants; 65 of 15,839 [0.41%]) or Group C (warfarin; 20 of 5006 [0.40%]) (Table 2). The ranges in all-cause mortality in studies of Groups A, B, and C were 0% to 0.62%, 0% to 0.29%, and 0.1% to 0.67%, respectively. The fixed and random effects model estimates of pooled all-cause mortality showed similar patterns (Table 2). Relative risks and corresponding 95% confidence intervals showed a more than twofold risk (fixed effects: A versus B, $p = 0.01$; B versus C, $p = 0.04$; random effects: A versus B, $p < 0.01$; B versus C, $p = 0.03$) of all-cause mortality for prophylaxis A or C compared with prophylaxis B (Table 3). No difference was seen for prophylaxis A versus C.

The rate of symptomatic nonfatal PE was higher ($p = 0.019$) in Group A (94 of 15,839 patients [0.60%]) than in Group B (25 of 7193 [0.35%]) (Table 2). The rates of nonfatal PE in Groups A, B, and C were 0% to 1.2%, 0% to 0.62%, and 0.1% to 0.8%, respectively. The fixed and random effects model estimates of pooled nonfatal PE had similar patterns (Table 2). Similar to all-cause mortality, relative risks and corresponding 95% confidence intervals showed a 60% to 70% increased risk (fixed effects: $p = 0.02$; random effects: $p = 0.04$) of nonfatal PE comparing prophylaxis A with prophylaxis B (Table 3). However, the relative risks were similar for prophylaxis B compared with C and for A compared with C.

Discussion

The current low rate of symptomatic PE and all-cause mortality after THA and TKA questions the need for the use of potent anticoagulants for thromboprophylaxis, as they carry a risk for morbidity and mortality associated with increased bleeding. In this study, we attempted to determine the incidence of all-cause mortality and symptomatic, nonfatal PE after elective primary THA and TKA, focusing on three different thromboprophylaxis regimens frequently used worldwide.

One of the limitations of our review was comparing outcomes between trials. The majority of the patients in Group A (potent anticoagulants) were in a randomized

Table 2. Fixed and random effect estimates for death and pulmonary embolism

Modality	Number	Events	Fixed effects		Random effects	
			Rate per 100	95% Confidence interval	Rate per 100	95% Confidence interval
Death						
A	15,838	65	0.410	0.300–0.520	0.360	0.216–0.503
B	7193	14	0.195	0.073–0.316	0.145	0.041–0.249
C	5006	20	0.399	0.204–0.594	0.332	0.100–0.563
Pulmonary embolism						
A	15,838	94	0.593	0.465–0.721	0.501	0.287–0.715
B	7193	25	0.347	0.196–0.499	0.310	0.168–0.451
C	5006	26	0.519	0.302–0.736	0.457	0.140–0.774

Table 3. Fixed and random effect estimates for relative risk between modalities

Comparison	Fixed effects			Random effects		
	Relative risk	95% Confidence interval	p Value	Relative risk	95% Confidence interval	p Value
Death						
A versus B	2.10	1.18–3.74	0.01	2.48	1.28–4.32	< 0.01
C versus B	2.05	1.03–4.05	0.04	2.29	1.06–4.96	0.03
A versus C	1.03	0.62–1.69	0.92	1.08	0.63–1.87	0.77
Pulmonary embolism						
A versus B	1.71	1.10–2.65	0.02	1.62	1.01–2.58	0.04
C versus B	1.50	0.86–2.59	0.15	1.47	0.82–2.64	0.19
A versus C	1.14	0.74–1.76	0.55	1.10	0.69–1.74	0.70

trial, whereas Group B (multimodal) consisted of cohort studies. Group C (warfarin) had randomized and nonrandomized studies (Table 1). Although randomized trials have a higher level of evidence than prospective cohorts, the listed randomized trials (Table 1) were systematically subject to exclusion of patients at high risk of venous thromboembolism, which could tend to reduce the mortality rate and thereby underestimate the mortality in a more representative population. On the other hand, the consecutive cohort studies used in our analysis represent a broader cross-section of patients and are likely more representative (Table 1) [47]. However, all-cause mortality is a defined end point and unlikely to be underreported. In addition, we do not report on the incidence of bleeding. Major local and/or systemic bleeding is not uniformly reported in the literature and therefore a uniform analysis of major bleeding complications may not be feasible or reliable. Instead, we focused on all-cause mortality, a valid, accepted surrogate to evaluate thromboprophylaxis. We included patients undergoing THA and TKA, although the pathogenesis of deep vein thrombosis is different between surgeries. In THA, venous stasis occurs intermittently and procoagulants are forced into the venous system predominantly during the femoral work [56]. If a tourniquet is used during TKA, venous stasis occurs throughout the procedure. The tourniquet may be a risk factor for thrombosis by means of causing endothelial damage [40]. However, these cases have a similar perioperative mortality rate (0%–0.67%) (Table 1) and the risk of bleeding from anticoagulation exists for both procedures. Finally, we included low-molecular weight heparin, ximelagatran, fondaparinux, and rivaroxaban as one group. We believe this is justifiable because the rates of nonfatal PE and mortality were similar for all three drugs (Table 1) and the risks of bleeding are common to all five drugs.

In the English literature, Murray et al. [39] performed a meta-analysis of all available studies of THA in which information about overall death rate or fatal PE had been included in studies published from the 1970s through the 1990s. The studies were categorized according to the pharmacologic prophylaxis (none, heparin, warfarin, aspirin, and dextran). Patients receiving unfractionated and low-molecular-weight heparin were combined. A total of 130,000 patients were included [39]. The fatal PE rate was 0.1% to 0.2% and the death rate was 0.3% to 0.4% irrespective of the pharmacologic prophylaxis. The study concluded there is not enough evidence in the literature to determine if pharmacologic thromboprophylaxis decreases the death rate after THA.

Freedman et al. [18] published a meta-analysis of thromboembolic prophylaxis after elective THA that included randomized, controlled trials published from 1966 to 1998. Fifty-two studies with 10,929 patients were included. Placebo and five prophylactic agents were evaluated (low-molecular-weight heparin, warfarin, aspirin, low-dose heparin, and pneumatic compression devices). There were no differences in the rates of fatal PE or all-cause mortality between the groups [18].

The previously discussed meta-analyses by Murray et al. [39] and Freedman et al. [18] are subject to limitations. They included patients who underwent THA over three decades during which the rate of mortality and fatal PE changed substantially [35]. In the review by Murray et al. [39], mechanical compression devices were used infrequently and it now is known these devices substantially diminish the rate of venous thromboembolism with or without adjuvant pharmacoprophylaxis [31, 41, 48]. Our review comprises THA and TKA studies published during the last 9 years to capture arthroplasties performed with the current anesthesia and surgical technique. We did not include patients receiving postoperative unfractionated heparin for prophylaxis because it has been associated with a high rate of bleeding [26] and is used only rarely today, being replaced by low-molecular-weight heparin and other forms of prophylaxis.

We observed Group A anticoagulants are associated with the highest mortality and Group B thromboprophylaxis (multimodal) is associated with the lowest all-cause mortality after total joint arthroplasty of the lower extremity. The reasons for this difference cannot be determined for certain, but a number of possibilities exist. Regional anesthesia may confer a benefit by itself. Regional anesthesia was used in 36% of patients in Group A and in 94% of patients in Group B. In a meta-analysis of anesthetic types, regional anesthesia was associated with a 30% reduction in mortality compared with general anesthesia in orthopaedic surgery [44]. However, this would not appear sufficient to explain the twofold difference. Perioperative mortality also is related to the surgeon and the case volume of each institution [28, 29]. All of the Group B studies were performed in high-volume centers, and some of the Group A and Group C (warfarin) studies may have been performed in low-volume centers. This might account for some of the differences observed between groups. Bleeding is more common with Group A anticoagulants. Bleeding [5, 8, 17, 18, 23, 26, 41, 42, 52, 55, 61] can lead to death from multiple causes, including shock, renal failure, stroke, myocardial infarction, infection, and sepsis. It is likely complications of bleeding contributed to the increased mortality. Furthermore, bleeding and risk of transfusion are less with regional compared with general anesthesia [46], especially if hypotensive epidural anesthesia is used [21].

We show clinical PE occurs despite the use of powerful anticoagulants. The rate of 0.6% is comparable to the rate of 1% previously described with warfarin [36] and low-molecular-weight heparin in cohort studies. This literature cannot support the use of powerful anticoagulants to prevent PE, although they clearly reduce the risk of venographically evident deep vein thrombosis [19].

We do not define the ideal thromboprophylaxis regime; rather, we show postoperative PE occurs despite the use of Group A anticoagulants and they may lead to higher mortality. It is possible lower doses of Group A anticoagulants, combined with regional anesthesia and pneumatic compression, could be efficacious. Nevertheless, any potential benefit must be balanced against the risk of bleeding. One potential benefit of Group A anticoagulants is the possibility that by reducing deep vein thrombosis, they may result in a lower risk of a subsequent postphlebitic syndrome. This was not evaluated in any of these studies and it is questionable whether the use of Group A anticoagulants can be justified on this basis alone.

One of the criticisms of pneumatic compression has been the poor compliance once patients begin walking. All of the studies we have included comprise patients operated on in recent years with reduced lengths of hospital stay in which pneumatic compression probably was used no more than 2 to 3 days [48]. It may be that pneumatic compression of short duration is sufficient prophylaxis, but this may require further study.

The recommendations from the Chest Physicians Consensus Statement advocate low-molecular-weight heparin or warfarin for prophylaxis after THA and TKA [19]. These recommendations often result in physicians feeling compelled to prescribe these anticoagulants to avoid potential litigation [30]. The increased risk of bleeding complications has encouraged several experienced surgeons who perform joint arthroplasty to emphasize caution in the use of these anticoagulants [5]. We believe the American College of Chest Physicians should reconsider their guidelines to reflect the fact that PE occurs despite the use of potent anticoagulants and may, in fact, expose patients to increased mortality after surgery.

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